Asymmetric Diels-Alder reactions with 5-menthyloxy-2(5H)-furanones

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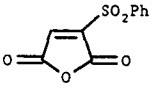
CHAPTER VI

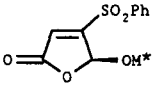
4-PHENYLSULFONYL SUBSTITUTED 5-ALKOXY-2(5H)-FURANONES; SYNTHESIS AND [4+2] CYCLOADDITIONS

6.1 *Introduction*

The work described in this chapter was inspired by the work of Hall and coworkers, who in 1989 published the synthesis of α-carbomethoxy-N-phenylmaleimide[1] and α-(phenylsulfonyl)maleic anhydride (6.1).[2,3] Especially the latter compound attracted our attention because of its high reactivity as dienophile in [4+2] cycloadditions. At room temperature both cyclopentadiene and 2,3-dimethyl-1,3-butadiene reacted in less than 1 minute with sulfone 6.1 to yield the Diels-Alder adducts in 100% yield.
Because of the high reactivity of this sulfone it would be of great interest to develop a chiral analogue of 6.1. We though that by the introduction of a sulfone substituent at the furanone ring of enantiomerically pure 5-menthyloxy-2(5H)-furanones, the dienophilic character could be increased considerable and that in this way the scope of diastereoselective Diels-Alder reactions could be extended. In our case we had two possibilities to synthesize a sulfonyl substituted 5-menthyloxy-2(5H)-furanone; either with a sulfonyl substituent at C_3 or at C_4. From a synthetic point of view the preparation of enantiomerically pure 5-menthyloxy-4-(phenylsulfonyl)-2(5H)-furanone (6.2) seemed to be most feasible.



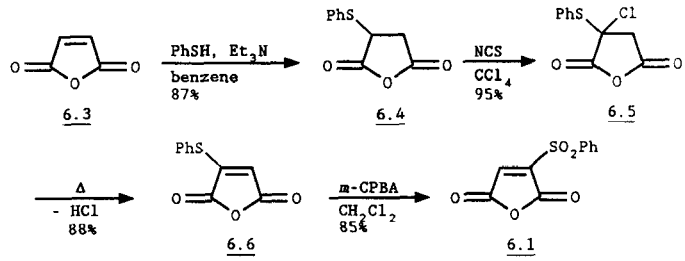
6.1



6.2

Figure 6.1

The synthesis of the "super-electrophile" 6.1, described by Hall *et al.*[3], starts with the nucleophilic addition of thiophenol to maleic anhydride (6.3) to form sulfide 6.4, which is then chlorinated to 6.5. Formation of the unsaturated sulfide 6.6 is achieved by the thermal elimination of HCl. Oxidation of 6.6 with *m*-chloroperbenzoic acid (*m*-CPBA) affords the sulfone 6.1 in 85% yield.

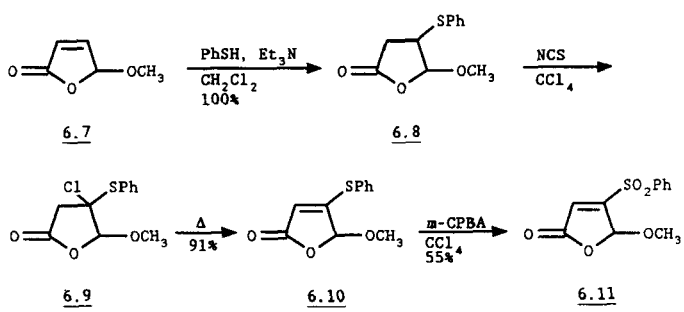


Scheme 6.1

6.2 *The synthesis of 5-alkoxy-4-(phenylsulfonyl)-2(5H)-furanones*

6.2.1 *The synthesis of racemic 5-methoxy-4-(phenylsulfonyl)-2(5H)-furanone*

For the synthesis of racemic 5-methoxy-4-(phenylsulfonyl)-2(5H)-furanone (6.11) we followed the same reaction sequence as for sulfone 6.1.



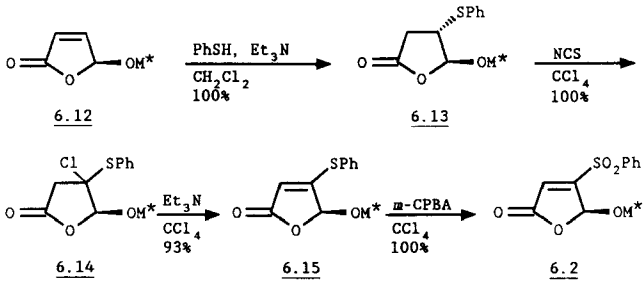
Scheme 6.2

Addition of thiophenol to racemic 5-methoxy-2(5H)-furanone (6.7), which is catalyzed by triethylamine,[4] afforded the sulfide 6.8 as a single diastereoisomer in quantitative yield. The ^{1}H NMR spectrum of 6.8 indicated that the addition of thiophenol had taken place diastereoselectively trans to the methoxy substituent at C_5 of the furanone ring. The addition product was used in the next reaction step without purification. Reaction of sulfide 6.8 with N-chlorosuccinimide (NCS) in refluxing carbon tetrachloride afforded the chlorinated compound 6.9. Because of its instability no efforts were made to isolate compound 6.9. The elimination of HCl was effected by heating

6.9 in an oil bath at 135 °C under reduced pressure (12 mm Hg). As judged from the ^{1}H NMR spectrum of the crude reaction product complete elimination of HCl had taken place within 15 minutes. Distillation of the reaction product (140 °C, 0.1 mm Hg) afforded the unsaturated sulfide 6.10 as a yellow oil in 87% overall yield. Compound 6.10 was also obtained by a direct distillation of 6.9 (150 °C, 0.001 mm Hg). In this way the unsaturated sulfide 6.10 is obtained in 91% overall yield starting from racemic 5-methoxy-2(5H)-furanone (6.7). Oxidation of sulfide 6.10 with 2 equivalents of *m*-CPBA in carbon tetrachloride produced sulfone substituted furanone 6.11 in 90% yield as a white crystalline compound, which was pure based on the ^{1}H and ^{13}C NMR spectra.

6.2.2 *The synthesis of enantiomerically pure (5S)-5-(d-menthyloxy)-4-(phenylsulfonyl)-2(5H)-furanone*

The synthesis of enantiomerically pure (5S)-5-(*d*-menthyloxy)-4-(phenylsulfonyl)-2(5H)-furanone (6.2) starts with the addition of thiophenol to (5S)-5-(*d*-menthyloxy)-2(5H)-furanone (6.12), which is catalyzed by triethylamine.[4]



Scheme 6.3

Product 6.13, which is obtained as a single diastereoisomer in 100% yield, was used in most cases in the next reaction step without purification, although it can be crystallized from *n*-hexane. The small coupling constant for the acetal hydrogen (J = 1.1 Hz) indicates that the menthyloxy group and the phenylthio group have a trans relationship to each other, which is in accordance with the expected addition of thiophenol to the less hindered side of furanone 6.12. Reaction of sulfide 6.13 with N-chlorosuccinimide in refluxing carbon tetrachloride afforded, as determined from the ^{1}H NMR spectrum, compound 6.14 in quantitative yield. Although several efforts were made, this compound could not be obtained in pure form, due to the elimination of HCl.

Compound 6.14 was therefore transformed into the unsaturated sulfide 6.15, without isolation. The elimination of HCl was achieved by prolonged refluxing of 6.14 in carbon tetrachloride to yield 6.15 in 85% yield, after crystallization from *n*-hexane. The time needed for complete elimination varied greatly between several hours to 6 days. Elimination at more elevated temperatures or *via* distillation under high vacuum, as described for 6.9, is less suitable in this case as at the high temperature needed, considerable epimerization of 6.15 takes place at the acetal stereogenic center.

Care should be taken that no acid catalyzed epimerization of furanone 6.15 occurs during the elimination of HCl. The best way to prevent this epimerization is to bubble air continuously through the refluxing solution, which results in a fast removal of HCl. Although in most cases the epimerization cannot be suppressed completely, it can be limited to a maximum of 10%. The undesired isomer of 6.15 can readily be removed by a single crystallization from *n*-hexane or petroleum-ether 40-60.

This procedure for the elimination of HCl was based on the results published by Hall *et al.*[3] The epimerization of 6.15 under these reaction conditions and the variable reaction times make this procedure less attractive and forced us to search for a more satisfactory route. The most obvious is the base induced elimination of HCl. Triethylamine was very suitable for this purpose. When the chlorination of 6.13 with N-chlorosuccinimide was directly followed by treatment of the adduct 6.14 with Et_3N, the unsaturated sulfide 6.15 was isolated in 93% yield. No isomerization was observed in this case. This procedure appeared to be also successful in the case of 4-chloro-5-(*d*-menthyloxy)-3-methyl-4-thiophenyl-2(5H)-furanone (6.39) (see Section 6.7).

The corresponding sulfone 6.2 was obtained in 100% yield by oxidation of sulfide 6.15 with 2 equivalents of *m*-chloroperbenzoic acid in carbon tetrachloride. The product was isolated by extraction of the reaction mixture with a saturated $NaHCO_3$ solution, followed by the addition of methyl sulfide. The solution was stirred until the peroxide test was negative.

The sulfone 6.2 is obtained as a highly viscous oil and cannot be crystallized from *n*-hexane or petroleum-ether 40-60. It is therefore of great importance that the sulfide 6.15 is diastereomerically pure before the oxidation with *m*-chloroperbenzoic acid is performed. During the oxidation step again the danger exists that under the acidic conditions an undesired epimerization of acetal center C_5 occurs. In the case of 6.2 the epimers can not easily be separated by means of crystallization or distillation. At the high temperatures needed for distillation also epimerization at the acetal center occurs.

To prevent epimerization during the oxidation of 6.15 with *m*-chloroperbenzoic acid the reaction was performed at a temperature of 0 °C, and the reaction time was kept as short as possible. As the reaction is performed in carbon tetrachloride its course can be followed easily by means of ^{1}H NMR spectroscopy. In the ^{1}H NMR spectrum the signal for the acetal hydrogen shifts from 5.34 ppm in the case of 6.15 to 6.28 ppm for 6.2. With higher reaction temperatures (room temperature) and extended reaction times (18 hours) substantial epimerization of 6.2 is observed (ratio of both diastereoisomers 60:40). This is readily deduced by means of ^{1}H NMR spectroscopy, as the acetal hydrogen of the epimer of sulfone 6.2 has an absorption at 6.19 ppm against 6.28 ppm for the sulfone 6.2. Also the hydrogen atoms at the C,C double bond show a significant difference in chemical shift; product 6.2 has an absorption at 6.77 ppm for C_{3H} and in the epimer C_{3H} is found at 6.61 ppm.

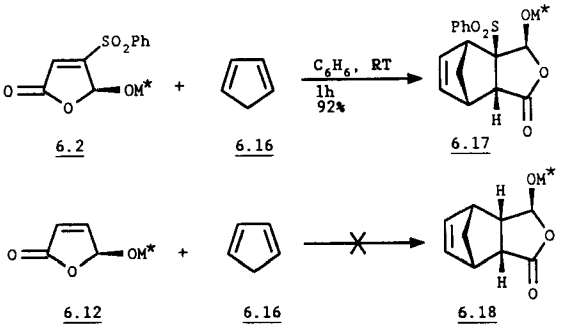
The epimer of sulfide 6.15 can be oxidized in the same way, yielding the epimer of sulfone 6.2 in 96% yield. In contrast to 6.2, which was obtained as a highly viscous oil, its C_5 epimer was obtained as a solid material that could be crystallized easily from *n*-hexane. The product was fully characterized by ^{1}H NMR and ^{13}C NMR spectroscopy.

Other oxidation reagents like sodium periodate or OXONE[5] (potassium peroxymonosulfate) were less successful. The oxidation of 6.15 with sodium periodate was carried out in a mixture of ethanol and water. After stirring for 24 hours at room temperature no oxidation of 6.15 could be observed. The use of OXONE is not recommended as the solution becomes very acidic (pH = 2-3), which may result in an epimerization at the acetal carbon C_5 or a hydrolysis of the furanone ring.

6.3 *Comparison of the reactivity of 5-menthyloxy-2(5H)-furanone and 5-menthyloxy-4-(phenylsulfonyl)-2(5H)-furanone in the Diels-Alder reaction with cyclopentadiene*

The reactivity of the 4-phenylsulfonyl substituted furanone 6.2 was studied in the reaction with cyclopentadiene (6.16). Both (5S)-5-(*d*-menthyloxy)-2(5H)-furanone (6.12) and (5S)-5-(*d*-menthyloxy)-4-(phenylsulfonyl)-2(5H)-furanone (6.2) were allowed to react with cyclopentadiene (6.16) for 0.5 h at room temperature in benzene. The ^{1}H NMR spectrum of the reaction mixture of the activated furanone 6.2 clearly showed that the starting material 6.2 had completely disappeared, and that only one cyclization product had been formed during the reaction. At 4.9 ppm a new signal had appeared, which is due to the acetal hydrogen of the expected cycloadduct 6.17. In the

case of (5S)-5-(*d*-menthyloxy)-2(5H)-furanone (6.12) only the starting material 6.12 was recovered. The ^{1}H NMR spectrum indicated that no cycloaddition had occurred under the reaction conditions mentioned above. This simple experiment therefore clearly demonstrates that the introduction of a sulfonyl substituent makes the furanone considerably more reactive in Diels-Alder reactions. The unfavorable steric effects of the phenylsulfonyl substituent in furanone 6.2 are overcome by the additional activation of the C,C double bond by the electron withdrawing sulfon substituent.

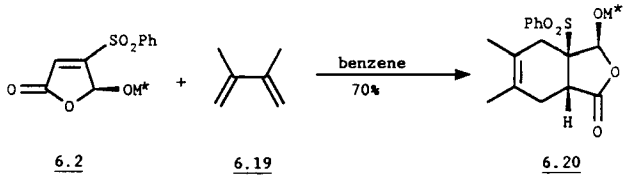


Scheme 6.4

6.4 *Diels-Alder reactions of 5-menthyloxy-4-(phenylsulfonyl)-2(5H)-furanone*

When the Diels-Alder reaction was repeated on a preparative scale the cycloaddition product 6.17 was obtained in 92% yield, after column chromatography. Compound 6.17 is most likely the *endo*-adduct of cyclopentadiene (6.16), as Hall *et al.*[3] have reported that in the reaction of cyclopentadiene with 6.1 exclusively the *endo*-adduct is being formed in 100% yield.

The cycloaddition reaction of 6.2 with 2,3-dimethyl-1,3-butadiene (6.19) was performed in refluxing benzene for 20 h, although a shorter reaction time may be sufficient for a complete conversion. After purification by flash column chromatography, product 6.20 was obtained as a white crystalline compound in 70% yield.



Scheme 6.5

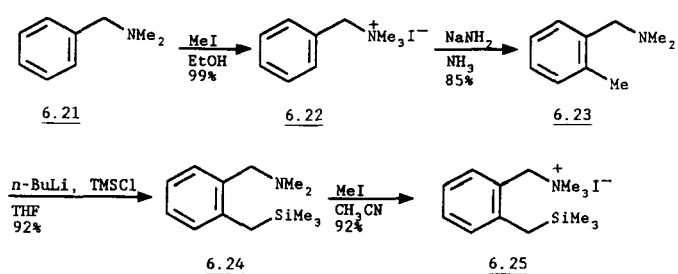
As judged from the ^{1}H and ^{13}C spectrum of 6.20, only one diastereoisomer was formed during the cycloaddition reaction.In analogy to the addition of 2,3-dimethyl-1,3-butadiene (6.19) to (5S)-5-(d-menthyloxy)-2(5H)-furanone (6.12), it is expected that also in the case of furanone 6.2, the addition of the diene is taking place from the less hindered side of the furanone ring, i.e. *trans* relative to the menthyloxy substituent.

6.5 *Diels-Alder reaction with o-xylylene*

Since its discovery, *o*-xylylene has been developed into a successful intermediate in organic synthesis. In the literature many procedures have been described for the generation of *o*-xylylene, for example, *via* the pyrolysis of benzocyclobutene or by elimination processes of 1,2-disubstituted benzene derivatives.[6] By trapping this highly reactive diene with a chiral trapping reagent, the synthesis of enantiomerically pure 2,3-disubstituted tetrahydronaphthalenes is feasible. We have prepared *o*-xylylene in two different ways, according to the procedure of Saegusa[7] and by the procedure of Boudjouk and Han.[8]

6.5.1 *The generation of o-xylylene according to the procedure of Saegusa*

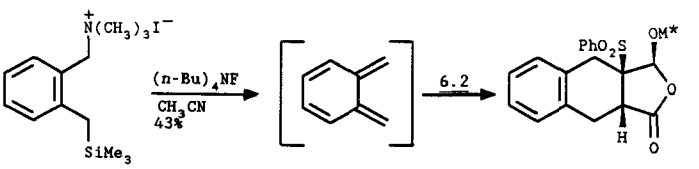
Saegusa *et al.*[7] have reported in 1982 the generation of *o*-xylylene from ammonium salt 6.25. Two important aspects of Saegusa's procedure for generating *o*-xylylene are first the fact that the generation of *o*-xylylene takes place at room temperature and second the possibility to lithiate and alkylate amine 6.24 at the position α to the Me_3Si group. By this means additional functionality and chirality can be introduced into the cycloaddition products. The synthetic route to 6.25 is outlined in Scheme 6.6.



Scheme 6.6

Reaction of N,N-dimethylbenzylamine (6.21) with methyl iodide afforded the quaternary ammonium salt 6.22 in 99% yield.[9] Treatment of 6.22 with a strong base, sodium amide in liquid ammonia, gave the rearranged product 6.23 in 85% yield.[10] Ortho-lithiation of 6.23 followed by trimethylsilyl chloride (TMSCl) afforded the silylated compound 6.24 in 92% yield, which was converted into quaternary ammonium salt 6.25 in 92% yield.

Treating a 1:1 mixture of compound 6.25 and furanone 6.2 with tetrabutylammonium fluoride in dichloromethane at room temperature afforded the cycloaddition product 6.27 in 43% yield as a solid compound. In this case *o*-xylylene (6.26) is formed by the fluoride induced 1,4-elimination of Me_3Si and Me_3N (Scheme 6.7). According to the ^1H and ^{13}C NMR spectra of 6.27, only one diastereoisomer had been formed during the cycloaddition reaction. The structure of 6.27 was assigned by extensive 2D COSY and NOESY NMR spectroscopy. The cross signal between the acetal hydrogen and one of the benzylic hydrogens observed in the NOESY spectrum clearly indicates the *trans* addition of the diene relative to the menthyloxy substituent of 6.2.



6.25 6.26 6.27

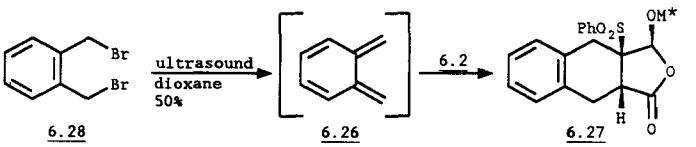
Scheme 6.7

When the same reaction was performed with 5-menthyloxy-2(5H)-furanone (6.12), no cycloaddition product was formed. In that case the reaction of 6.12 with the highly reactive *o*-xylylene (6.26) is probably not fast enough which results in the dimerization and polymerization of diene 6.26.[7,8,11] With the more reactive furanone 6.2, the polymerization can be suppressed successfully.

6.5.2 *The generation of o-xylylene according to the procedure of Boudjouk and Han*

Ortho-xylylene (6.26) can also be prepared by reaction of α,α'-dibromo-*o*-xylene (6.28) with activated zinc.[8] Under ultrasound conditions and in the presence of furanone 6.2 the cycloadduct 6.27 was obtained in 50% yield. Again a single diastereoisomer was formed during the cycloaddition reaction, with the same physical and spectroscopic

data as 6.27, obtained using the procedure of Saegusa for the generation of *o*-xylylene (6.26) (*vide supra*). This reaction must be performed under a nitrogen atmosphere to maintain a good quality of activated zinc.



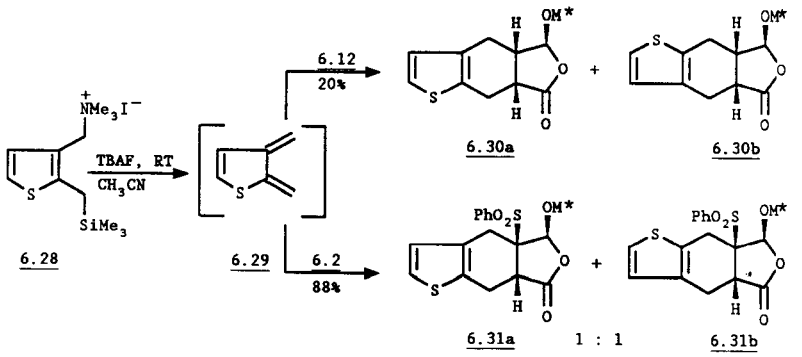
6.28 6.26 6.27

Scheme 6.8

When the reaction is not performed under a nitrogen atmosphere or with unactivated zinc, no *o*-xylylene (6.26) and consequently no cycloadduct is formed at all. Probably zinc oxide prevents reaction between dibromide 6.28 and zinc.

6.6 Diels-Alder reaction with 2,3-dimethylene-2,3-dihydrothiophene

The synthesis of the heterocyclic analog 6.29 of *o*-xylylene, was developed by Van den Berg and Van Leusen.[12] This diene has been used in cycloaddition reactions with several dienophiles, like dimethyl fumarate and dimethyl maleate. For further study of the effect of an additional sulfonyl substituent on the butenolide reactivity we also examined diene 6.29 in the [4+2] cycloaddition with (5R)-5-(*d*-menthyloxy)-2(5H)-furanone (6.12) and (5R)-5-(*d*-menthyloxy)-4-(phenylsulfonyl)-2(5H)-furanone (6.2). Both reactions were performed at room temperature by the slow addition of tetra-butylammonium fluoride, dissolved in acetonitrile, to a 1:1 mixture of precursor 6.28 and furanones 6.12 or 6.2. In the cycloaddition reaction with 2,3-dimethylene-2,3-dihydrothiophene (6.29) the same dramatic difference (see Section 6.3) between sulfonated furanone 6.2 and menthyloxy-2(5H)-furanone (6.12) was observed. Reaction of diene 6.29 with furanone 6.12 (1.0 equivalent) mainly gave dimeric products of 6.29, in addition to unreacted furanone 6.12. On the basis of ^{1}H NMR analysis about 20% of the crude reaction product consisted of [4+2] adducts 6.30a and 6.30b. However, formation of diene 6.29 in the presence of 1 equivalent of 6.2 gave the [4+2] cycloadducts 6.31a and 6.31b (a mixture of regioisomers in a 1:1 ratio) in 88% isolated yield. As diene 6.29 shows much similarity with diene 6.26 it is expected that the addition of 6.29 also takes place trans relative to the menthyloxy substituent of 6.2. Attempts to separate both regioisomers by crystallization or flash chromatography were not successful.

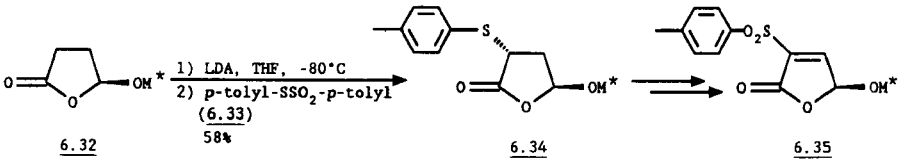


Scheme 6.9

The fact that two regioisomers were found is consistent with the results obtained with other unsymmetric dienophiles.[12] In the case of the reaction between 6.29 and methyl acrylate a mixture of two regioisomers was isolated with a ratio of 1.8:1., whereas with acrylonitrile as the dienophile the ratio was 2.4:1.

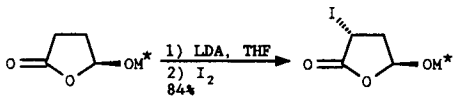
6.7 *Preliminary experiments for the synthesis of 5-menthyloxy-3-tolylsulfonyl-2(5H)-furanone*

Some preliminary experiments were performed to develop the synthesis of a diastereomerically pure 5-menthyloxy-2(5H)-furanone derivative 6.35 with a phenylsulfonyl substituent at C_3 of the furanone ring. As described in Chapter III, compound 6.32 was prepared in high yield by a hydrogenation of diastereomerically pure 5-menthyloxy-2(5H)-furanone (6.12). By lithiation of 6.32 and quenching of the enolate-anion of 6.32 with thiosulfonic S-ester 6.33, compound 6.34 was obtained in 58% yield. The ^{1}H NMR spectrum indicated that the main diastereoisomer of 6.34 had been formed with a selectivity of >90:10. However, chlorination of 6.34 with N-chlorosuccinimide was not successful.



Scheme 6.10

We were able, however, to introduce a halogen atom at the α-position of the carbonyl of compound 6.32 *via* lithiation of 6.32 and quenching the anion with iodine. This procedure yielded α-iodo-furanone 6.36 in 84% yield.



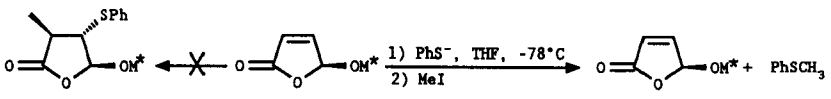
6.32 6.36

Scheme 6.11

Combination of these two reactions, followed by introduction of the C,C double bond and oxidation of the sulfide with 2 equivalents of *m*-CPBA might lead to the synthesis of diastereomerically pure 5-menthyloxy-3-tolylsulfonyl-2(5H)-furanone (6.35).

6.8 *The synthesis of diastereomerically pure (5S)-5-(d-menthyloxy)-3-methyl-4-(phenylsulfonyl)-2(5H)-furanone*

We have shown in the previous section that the reactivity of the furanone used as a dienophile in the [4+2] cycloaddition reactions, can be enhanced significantly by the introduction of a sulfonyl group at C_4. At the same time we have shown in Chapter III that 5-menthyloxy-3-methyl-2(5H)-furanone (6.37) has a very low reactivity in Diels-Alder reactions and that no quaternary stereogenic centers could be formed in this way. The question was if, by the introduction of a phenylsulfonyl group at C_4, the reactivity of 3-alkyl-furanones could be increased to such an extent that in subsequent Diels-Alder reactions products with quaternary stereogenic centers can be formed. Therefore several efforts were made to synthesize (5S)-5-(*d*-menthyloxy)-3-methyl-4-phenylsulfonyl-2(5H)-furanone (6.41). The first attempt was the simultaneous introduction of the alkyl substituent at C_3 and the sulfide substituent at C_4 to provide 6.38. However, at -78 °C the anion of thiophenol failed to give a 1,4-addition to (5S)-5-(*d*-menthyloxy)-2(5H)-furanone (6.12).



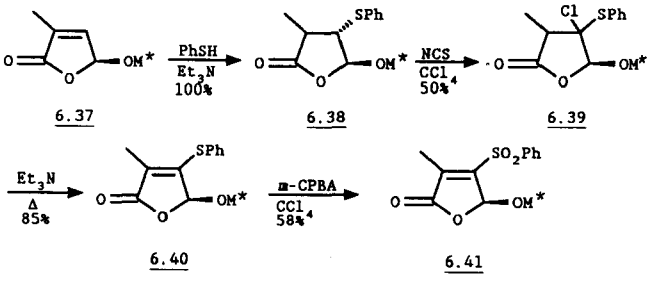
6.38 6.12 6.12

Scheme 6.12

After the addition of methyl iodide, in order to quench the enolate anion, and workup, (5R)-5-(*d*-menthyloxy)-2(5H)-furanone (6.12) was recovered, together with methyl phenyl sulfide.

The second attempt was a step by step approach. First thiophenol was added, in the presence of a catalytic amount of triethylamine, to 5-menthyloxy-2(5H)-furanone (6.12) (see Section 6.2) yielding compound 6.13 in 100% yield. The Michael adduct was then treated with LDA at low temperature (-80 °C) in THF and the enolate anion was subsequently quenched with methyl iodide. However, after work-up the expected adduct 6.38 could not be isolated. ^{1}H NMR analysis showed that under these conditions a retro Michael addition had taken place and that the product which had been formed was methyl phenyl sulfide. An explanation for this result might be a shift of the equilibrium of the thiophenol addition to the butenolide and the thiophenol anion, while the thiophenol anion is quenched more readily than the enolate anion.

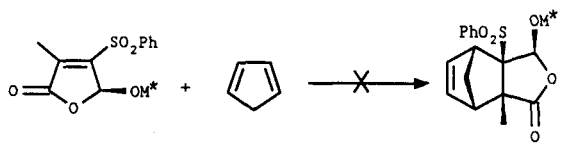
A successful route to 6.41 starts from diastereomerically pure 5-menthyloxy-3-methyl-2(5H)-furanone (6.37). De Lange had found that at room temperature, in dichloromethane and with a catalytic amount of triethylamine, the addition of thiophenol to 5-menthyloxy-3-methyl-2(5H)-furanone (6.37) gave a mixture of starting material (30%) and product 6.38, which consisted of a mixture of 2 diastereoisomers (ratio 65:35). The ^{1}H NMR spectrum of 6.38 showed that both compounds had a trans relationship between the thiophenol substituent at C_4 and the menthyloxy substituent at C_5, which means that the epimeric center is the carbon atom (C_3) of the furanone ring bearing the methyl substituent.



Scheme 6.13

Because of the incomplete conversion to 6.38 found by De Lange we performed the 1,4-addition of thiophenol to 5-menthyloxy-3-methyl-2(5H)-furanone (6.37), which is catalyzed by triethylamine, without solvent. Based on the ^{1}H NMR spectrum of the crude reaction mixture now a complete conversion to 6.38 had occurred. Chlorination

at C_4 of the lactone 6.38 with N-chlorosuccinimide in carbon tetrachloride, afforded compound 6.39 in 50% overall yield. Based on the ^1H NMR and ^{13}C NMR spectra of 6.39 only one diastereoisomer had been formed during these reactions. However, the absolute stereochemistry could not be established by means of a NOESY experiment. No cross signals were observed between, for example, the protons of the phenylthio group of the molecule and the menthyloxy substituent of the furanone ring. Furthermore, no cross signal was found between the methyl substituent at C_3 and the phenyl ring. HCl elimination was accomplished by heating 6.39 for 15 minutes in refluxing triethylamine, yielding 85% of product 6.40. The synthesis of dienophile 6.41 was completed by the oxidation of 6.40 with 2 equivalents of *m*-chloroperbenzoic acid. Compound 6.41 was obtained as a white crystalline compound in 58% yield as a single diastereoisomer, according to the ^1H NMR and ^{13}C NMR spectra. During the complete reaction sequence to 6.41 no epimerization at the acetal center was observed.



6.41 6.16 6.42

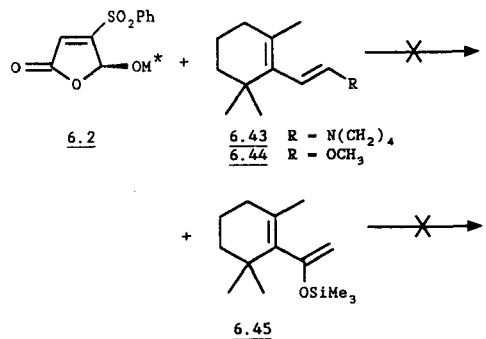
Scheme 6.14

Preliminary experiments towards the cycloaddition of 6.41 with cyclopentadiene (6.16) were examined. Heating both compounds for 24 h in toluene did not, however, afford cycloaddition product 6.42. Dienophile 6.41 was recovered unchanged.

6.9 Further attempts towards the synthesis of warburganal

As was described in Chapter V, several of our attempts to prepare the warburganal skeleton were not successful. One reason for the unsuccessful Diels-Alder reactions might be the low reactivity of 5-menthyloxy-2(5H)-furanone (6.12) towards the dienes like 6.43 and 6.44. It might be possible to synthesize Warburganal and related compounds with the more reactive furanone 6.2. Three types of activated dienes were tried in the Diels-Alder reaction with furanone 6.2. The reactions with dienes 6.43 and 6.44 were performed in refluxing toluene for 20 h. In neither case could product be isolated. In the reaction with diene 6.44 both starting materials were recovered. With diene 6.45, which has the opposite polarization of the HOMO compared to dienes

6.43 and 6.44, the opposite regioselectivity in the cycloaddition reaction with 6.2 is expected. In that case the unfavorable non-bonding interactions between the menthyloxy group of 6.2 and the cyclohexene ring of the diene are minimal. But it appeared that also this diene was not reactive enough for a successful Diels-Alder reaction. After heating furanone 6.2 with diene 6.45 for 3 days at 80 °C in benzene, the starting materials were recovered. Raising the temperature to 140 °C (refluxing xylene) had no effect. Also in this case no cycloaddition product was isolated.



6.2

6.43 R = $N(CH_2)_4$
6.44 R = OCH_3

6.45

Scheme 6.15

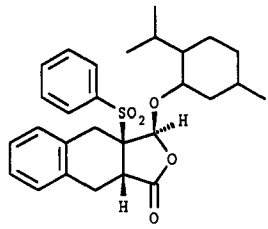
6.10 *Gel formation of 6.27 in alkanes*

During our attempts to crystallize compound 6.27 from *n*-hexane, which was successful as solvent for the crystallization of most compounds we have synthesized, we observed an unexpected phenomenon. When the hot solution of 6.27 was cooled to ambient temperature, no crystallization process was observed like in the case of compounds 6.17, 6.20 or 6.31. Instead, gel formation was observed.When the cooling process was performed in a sealed Pyrex tube, and when, after cooling in an ice bath, the gel was allowed to warm to ambient temperatures the sample did not flow perceptibly when inverted. When the solution is cooled slowly to room temperature an almost transparent gel was formed. In a sealed Pyrex test tube the gel can be stored for several days without separation into a solid and a liquid phase. Only on prolonged standing, up to three weeks, a separation into two phases was observed. At lower concentrations of 6.27, cooling with an ice bath is needed in order to reach the same effect.
The gelation is not limited to *n*-hexane. In other hydrocarbons, like pentane, heptane, cyclohexane or petroleum-ether 40-60, the same phenomenon was observed.

Table 6.1: Ratios of compound 6.27 *vs* various hydrocarbons at gel formation

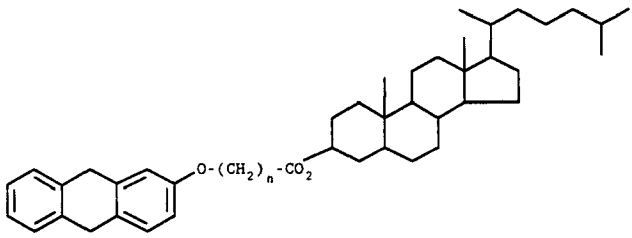
Solvent	Ratio (w/v)	Ratio (mol/mol)
pentane	1:50	1:200
n-hexane	1:225	1:825
cyclohexane	1:90	1:400
petroleum-ether 40-60	**	**

** Not determined



6.27

Table 6.1 shows the preliminary experimental results. With pentane is it very hard to get all the solid material into solution due to the low boiling point of this solvent (35 °C). With cyclohexane a gel was formed after cooling in an ice bath, with a ratio of 6.27 *vs* solvent of 1:90 (w/v). With *n*-hexane this ratio was 1:225 (w/v). This means that statistically each molecule of 6.27 can form a gel with more than 825 molecules of *n*-hexane. With pentane each molecule of 6.27 can form a gel with up to 200 molecules of the solvent. These numbers are comparable with those reported by Weiss *et al*,[13] who investigated for the first time gel formation with low molecular compounds in organic solvents. With compounds of the type 6.46, which are known to form liquid crystals,[14,15] ratios of 1:500 (mol/mol) were reached.



6.46

Figure 6.2

Gel formation of 6.46 occurs in a variety of solvents like pentane, hexane, dodecane, propanol, octanol, 4-heptanol, etc. The ^1H NMR spectrum of 6.27, recorded in C_6D_{12} (deuterocyclohexane) at 60 °C, does not show perceptible line broadening. However, when the temperature was lowered to 15 °C, the signals of compound 6.27 almost completely collapsed with considerable line broadening.

At this moment we do not know what the influence is of different substituents at the

naphthofuranone ring of 6.27, or how important the absolute configuration at the acetal center is for the gel formation. Perhaps these gels can be formed using racemic naphthofuranones, with a methoxy substituent instead of the menthyloxy group.
So far we have no clear explanation for the gelling of alkanes with 6.27. One explanation might be that the aromatic part of the naphthofuranones are stacked, forming rod-like structures or fibers. Electron microscopy studies might reveal details of the structures of the gels. However, very little precedent exist about the formation of such ordered supramolecular structures or chiral gels.

6.11 *Conclusions*

In this chapter we have shown that racemic 5-methoxy-4-(phenylsulfonyl)-2(5H)-furanone is readily accessible and in high yield by a number of simple reactions in 50% overall yield starting from 6.7. Furthermore we have shown that, by starting from diastereomerically pure 5-menthyloxy-2(5H)-furanone (6.12), diastereomerically pure 5-menthyloxy-4-(phenylsulfonyl)-2(5H)-furanone (6.2) is readily available in high yield (93% overall) by the same sequence. As was expected on the basis of the results obtained by Hall *et al.*,[3] dienophile 6.2 was indeed considerably more reactive in [4+2] cycloadditions than the unsubstituted furanone 6.12. The cycloaddition reactions with 6.2 afforded diastereomerically pure Diels-Alder adducts in high yield. The scope of the cycloadditions with 5-menthyloxy-2(5H)-furanones was extended to the reactions with highly reactive and highly unstable dienes like *o*-xylylene and its heterocyclic analogue 2,3-dimethylene-2,3-dihydrothiophene. Another advantage of furanone 6.2 might be the possibility of elimination of the phenylsulfonyl substituent in the Diels-Alder adducts. This might, for example, be a way to introduce a C,C double bond which is conjugated to the C=O of the lactone ring in the Diels-Alder adducts. By the same reaction sequence as mentioned above we were able to synthesize furanone 6.41, with an additional methyl substituent at C_3 of the furanone ring. One preliminary experiment showed low reactivity of this compound in the cycloaddition reaction with cyclopentadiene. This is presumably due to steric hindrance as a methyl group is introduced at a bridgehead position during the Diels-Alder reaction.

For general remarks see Section 2.5. For the preparation of dienes 6.43-6.45 see Chapter V.

5-Methoxy-4-(phenylthio)-2(5H)-furanone (6.10)

5-Methoxy-2(5H)-furanone (6.7) (5.00 g, 43.9 mmol) and thiophenol (5.00 g, 45.5 mmol) were dissolved in CH_2Cl_2 (25 mL), 3 drops of Et_3N were added, and the mixture was stirred at room temperature. After 1 h the solvent was removed under reduced pressure and the excess thiophenol was removed by bulb-to-bulb distillation under high vacuum yielding dihydro-5-methoxy-4-(phenylthio)-2(3H)-furanone (6.8) in 100% yield. ^1H NMR ($CDCl_3$, 300 MHz): δ 2.38 (dd, J = 2.93, 18.68 Hz, 1H), 3.02 (dd, J = 8.42, 18.68 Hz, 1H), 3.37 (s, 3H), 3.77 (ddd, J = 1.47, 2.93, 8.42 Hz, 1H), 5.20 (d, J = 1.47 Hz, 1H), 7.30 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 33.25 (t), 45.76 (d), 56.43 (q), 107.81 (d), 127.54 (d), 128.99 (d), 131.11 (d), 131.77 (s), 173.55 (s).
Compound 6.8 (9.00 g, 40.2 mmol) and N-chlorosuccinimide (5.40 g, 40.4 mmol) were dissolved in CCl_4 (100 mL). After refluxing for 0.5 h, the reaction mixture was cooled in an ice bath and the precipitate, which had been formed, was removed by filtration. After evaporation of the solvent under reduced pressure, the residue was heated under reduced pressure (12 mm Hg) for 15 min. on an oil bath at 135 °C. Based on ^1H NMR a complete elimination of hydrogen chloride had occurred. The crude product was purified by bulb-to-bulb distillation (140 °C, 0.1 mm Hg) yielding compound 6.10 (7.80 g, 80%) as a yellow oil. ^1H NMR ($CDCl_3$, 300 MHz): δ 3.38 (s, 3H), 5.22 (s, 1H), 5.68 (s, 1H), 7.35 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 55.03 (q), 101.79 (d), 112.28 (d), 126.78 (s), 129.50 (d), 129.86 (d), 133.71 (d), 166.83 (s), 167.80 (s); HRMS calcd 222.035, found 222.036.

5-Methoxy-4-(phenylsulfonyl)-2(5H)-furanone (6.11)

Sulfide 6.10 (9.07 g, 40.5 mmol) was dissolved in carbon tetrachloride (250 mL). After the addition of *m*-chloroperbenzoic acid (17.40 g, 80.7 mmol) the solution was stirred for 1 h at room temperature. The organic solvent was extracted with a saturated $NaHCO_3$ solution (2 x 100 mL), dried over $MgSO_4$, filtered and the solvent evaporated under reduced pressure. The solid material was dissolved in a mixture of *n*-hexane and CH_2Cl_2 and filtered over a short pad of silica gel. After evaporation of the solvent product 6.11 (5.75 g, 55%) was obtained as a white crystalline compound which could be recrystallized from octane. Mp 96.8-98.3 °C. ^1H NMR ($CDCl_3$, 300 MHz): δ 3.42 (s, 3H), 6.02 (d, J = 1.1 Hz, 1H), 6.72 (d, J = 1.1 Hz, 1H), 7.61 (m, 2H), 7.72 (m, 1H), 7.69 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 57.19 (q), 102.00 (d), 129.04 (d), 129.62 (d), 135.27 (d), 137.46 (s), 161.51 (s), 165.94 (s); HRMS calcd 254.025, found 254.025; Anal Calcd. for $C_{11}H_{10}O_5S$: C, 51.96; H, 3.96. Found: C, 51.75; H, 3.86.

[1R[1α(4R*,5R*),2β,5α]]-Dihydro-5-[[5-methyl-2-(1-methylethyl)cyclohexyl]oxy]-4-(phenylthio)-2(3H)-furanone (6.13)

(5R)-5-(*l*-Menthyloxy)-2(5H)-furanone (6.12) (4.76 g, 20.0 mmol) was dissolved in CH_2Cl_2 (30 mL). After the addition of thiophenol (2.42 g, 22.0 mmol) and 3 drops of Et_3N the solution was stirred for 1 h at room temperature. After evaporation of the solvent the product 6.13 (6.69 g, 100%) was obtained as a single diastereoisomer.

Analytically pure product was obtained by crystallization from *n*-hexane. Yield 91%. Mp 78.3-79.0 °C. $[\alpha]^{20}_D$ -60.6° (c 1.00, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 0.67-1.00 (m, 12H), 1.15 (m, 1H), 1.26 (m, 1H), 1.58 (m, 1H), 1.79 (m, 1H), 1.98 (ddd, J = 2.57, 6.96, 13.92 Hz, 1H), 2.41 (dd, J = 2.57, 18.31 Hz, 1H), 3.07 (dd, J = 8.42, 8.42 Hz, 1H), 3.43 (dt, J = 4.03, 10.62 Hz, 1H), 3.79 (ddd, J = 1.10, 2.57, 8.42 Hz, 1H), 5.48 (d, J = 1.10 Hz, 1H), 7.24-7.39 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 15.41 (q), 20.66 (q), 21.95 (q), 22.85 (t), 25.29 (d), 31.04 (t), 33.58 (t), 33.99 (d), 39.46 (t), 46.25 (d), 47.43 (d), 77.47 (d), 103.81 (d), 127.67(d), 129.17 (d), 131.31 (d), 132.32 (s), 174.05 (s); HRMS calcd 348.176, found 348.175; Anal Calcd. for $C_{20}H_{28}O_3S$: C, 68.93; H, 8.10; S, 9.20. Found: C, 68.98; H, 8.01; S, 9.23.

[1S[1α(S*),2β,5α]]-5-[[5-Methyl-2-(1-methylethyl)cyclohexyl]oxy]-4-(phenylthio)-2(5H)-furanone (6.15)

Procedure A:

Compound 6.13 (4.56 g, 13.1 mmol) was dissolved in carbon tetrachloride (50 mL). After the addition of N-chlorosuccinimide (1.92 g, 14.4 mmol) the solution was refluxed until the chlorination was completed (determined by ^1H NMR spectroscopy). While air was bubbled through the solution reflux was continued until the elimination of hydrogen chloride had been completed (determined by ^1H NMR spectroscopy). The reaction mixture was cooled in an ice-water bath and the precipitated succinimide was removed by filtration. Evaporation of the solvent left crude 6.15 as a white solid. After crystallization from *n*-hexane diastereomerically pure 6.15 (3.85 g, 85%) was obtained. Mp 116.7-117.7 °C; $[\alpha]^{20}_D$ +79.3° (c 1.00, CH_2Cl_2); ^1H NMR ($CDCl_3$, 300 MHz): δ 0.78-1.08 (m, 12H), 1.14 (m, 2H), 1.66 (m, 2H), 2.03 (m, 1H), 2.18 (m, 1H), 3.63 (dt, J = 4.2, 11.1 Hz, 1H), 5.34 (s, 1H), 5.95 (s, 1H), 7.45 (m, 3H), 7.57 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 15.53 (q), 20.70 (q), 22.03 (q), 22.84 (t), 24.97 (d), 31.28 (d), 33.95 (t), 40.08 (t), 47.30 (d), 79.70 (d), 99.56 (d), 112.54 (d), 127.6 (s), 129.81 (d), 130.10 (d), 134.13 (d), 167.78 (s), 168.75 (s); HRMS calcd 346.160, found 346.158; Anal. Calcd for $C_{20}H_{26}O_3S$: C, 69.33; H, 7.56; S, 9.25. Found: C, 68.99; H, 7.48; S, 9.16.

Procedure B:

A mixture of compound 6.13 (2.38 g, 6.84 mmol) and N-chlorosuccinimide (1.00 g, 7.49 mmol) was refluxed in carbon tetrachloride (25 mL) until the starting material had disappeared (determined by ^1H NMR spectroscopy). The solution was cooled in an ice bath and the precipitated succinimide was removed by filtration. After the addition of Et_3N (10 mL) the solution was stirred for 15 min at room temperature and extracted with water. The organic layer was dried over Na_2SO_4, filtered and the solvent evaporated under reduced pressure, yielding product 6.15 (2.21 g, 93%) as a slightly yellow crystalline compound. The ^1H NMR spectrum, which was identical with the one obtained in procedure A, showed that no epimerization had occurred during the reaction.

[1S[1α(S*),2β,5α]]-5-[[5-Methyl-2-(1-methylethyl)cyclohexyl]oxy]-4-(phenylsulfonyl)-2(5H)-furanone (6.2)

A stirred solution of compound 6.15 (5.30 g, 15.3 mmol) in carbon tetrachloride (50 mL) was cooled to 4 °C. While the temperature was maintained below 5 °C, small portions of *m*-CPBA (6.96 g, 34.8 mmol) were added. According to the ^1H NMR

spectrum of the reaction mixture a complete conversion to sulfonyl 6.2 had taken place within 15 minutes. The organic solution was extracted with a saturated $NaHCO_3$ solution and methyl sulfide was added. The solution was stirred until the peroxide test was negative. The organic layer was dried over $MgSO_4$, filtered and the solvent was evaporated under reduced pressure. Product 6.2 (5.84 g, 101%) was obtained as a highly viscous colorless oil, which was pure according to ^1H NMR. Further purification of 6.2 can be effected by column chromatography (SiO_2/CH_2Cl_2). After rigorous attempts some material could be crystallized from *n*-hexane to yield analytically pure 6.2. Mp 77.1-78.5 °C; $[\alpha]^{20}_D$ +123.4° (c 1.34, CH_2Cl_2); ^1H NMR ($CDCl_3$, 300 MHz): δ 0.55-0.96 (m, 13H), 1.28 (m, 1H), 1.56 (m, 3H), 2.13 (m, 1H), 3.48 (dt, J = 4.2, 10.1 Hz, 1H), 6.22 (d, J = 0.9 Hz, 1H), 6.72 (d, J = 0.9 Hz, 1H), 7.51 (m, 2H), 7.64 (m, 1H), 7.97 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 15.48 (q), 20.34 (q), 21.99 (q), 22.94 (t), 24.92 (d), 31.13 (d), 33.91 (t), 38.92 (t), 47.46 (d), 79.19 (d), 97.65 (d), 128.76 (d), 128.89 (d), 128.98 (d), 134.58 (d), 137.69 (s), 161.92 (s), 166.10 (s); HRMS could not be determined as M^+ was not observed; Anal. Calcd for $C_{20}H_{26}O_5S$: C, 63.47; H, 6.92; S, 8.47. Found: C, 62.98; H, 6.94; S, 8.46.

Oxidation of the epimer of 6.15
[1S[1α(R*),2β,5α]]-5-[[5-methyl-2-(1-methylethyl)cyclohexyl]oxy]-4-(phenylsulfonyl)-2(5H)-furanone

During a large scale preparation of diastereomerically pure 6.15, *via* the thermal HCl elimination of 6.14, the product was isolated as a mixture of epimers (ratio 60:40). A single crystallization from heptane afforded in this case the epimer of 6.15 as white needles. Mp 138.5-139.0 °C; $[\alpha]^{20}_D$ -3.3° (c 1.00, CH_2Cl_2); ^1H NMR ($CDCl_3$, 300 MHz): δ 0.81-1.17 (m, 3H), 0.84 (d, J = 7.0 Hz, 3H), 0.92 (d, J = 7.0 Hz, 3H), 0.95 (d, J = 7.0 Hz, 3H), 1.40 (m, 2H), 1.68 (m, 2H), 2.32 (m, 2H), 3.55 (dt, J = 4.4, 10.6 Hz, 1H), 5.27 (s, 1H), 5.87 (s, 1H), 7.46 (m, 3H), 7.56 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 15.55 (q), 20.65 (q), 21.78 (q), 22.52 (t), 24.97 (d), 31.21 (d), 33.71 (t), 41.97 (t), 47.66 (d), 83.44 (d), 103.03 (d), 112.08 (d), 127.47 (s), 129.69 (d), 129.95 (d), 133.81 (d), 167.89 (s), 168.25 (s); HRMS calcd 346.160, found 346.158; Anal. Calcd for $C_{20}H_{26}O_3S$: C, 69.33; H, 7.56; S, 9.25. Found: C, 69.09; H, 7.58; S, 9.23.

This epimer was oxidized in the same way as described for 6.15 (*vide supra*). To a stirred solution of the epimer of sulfide 6.15 (1.00 g, 2.87 mmol) in CH_2Cl_2 (20 mL) was added *m*-chloroperbenzoic acid (80% pure) (1.31 g, 6.07 mmol) while the temperature is maintained at 0 °C. After stirring for 0.5 h, methyl sulfide (1 mL) was added and stirring was continued until the peroxide test was negative. The organic solution was extracted with a saturated $NaHCO_3$ solution (2 x 25 mL), dried over $NaHCO_3$, filtered and the solvent evaporated under reduced pressure, yielding product 6.2 (1.05 g, 96%) as a white solid. Analytically pure product could be obtained by crystallization from pentane. Mp 84.4-85.0 °C; $[\alpha]^{20}_D$ +36.7° (c 1.00, CH_2Cl_2); ^1H NMR ($CDCl_3$, 300 MHz): δ 0.64-0.95 (m, 3H), 0.73 (d, J = 6.9 Hz, 3H), 0.81 (d, J = 5.9 Hz, 3H), 0.83 (d, J = 7.0 Hz, 3H), 1.05 (m, 1H), 1.29 (m ,1H), 1.57 (m, 2H), 2.07 (m, 2H), 3.51 (dt, J = 4.4, 10.6 Hz, 1H), 6.13 (d, J = 0.7 Hz, 1H), 6.56 (s, 1H), 7.53 (m, 2H), 7.66 (m, 1H), 7.85 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 15.47 (q), 20.89 (q), 21.85 (q), 22.33 (t), 24.28 (d), 31.33 (d), 33.59 (t), 41.81 (t), 47.81 (d), 83.17 (d), 101.77 (d), 128.17 (d), 129.13 (d), 129.19 (d), 134.62 (d), 137.66 (s), 161.46 (s), 165.90 (s); HRMS could not be determined as M^+ was not observed; Anal. Calcd for

$C_{20}H_{26}O_5S$: C, 63.47; H, 6.92; S, 8.47. Found: C, 63.41; H, 6.87; S, 8.44.

Attempted oxidation of sulfide 6.15 with sodium periodate

Compound 6.15 (346 mg, 1.0 mmol) and $NaIO_4$ (428 mg, 2 mmol) were dissolved in a mixture of water (2 mL) and ethanol (10 mL). After stirring for 24 h at room temperature, water was added and the solution was extracted with ether. The combined organic layers were dried over Na_2SO_4, filtered and evaporated under reduced pressure. The ^1H NMR spectrum of the crude reaction mixture showed that no oxidation had occurred.

[3R-[3α(1R*,2S*,5R*),3aα,4α,7α,7aα]]-3a,4,7,7a-Tetrahydro-3-[[5-methyl-2-(1-methylethyl)cyclohexyl]oxy]-3a-(phenylsulfonyl)-4,7-methanoisobenzofuran-1(3H)-one (6.17)

A solution of compound 6.2 (360 mg, 0.95 mmol) and cyclopentadiene (6.16) (629 mg, 9.50 mmol) in dry toluene (10 mL) was stirred for 1 h at room temperature. After evaporation of the solvent under reduced pressure the crude product was purified by flash column chromatography (SiO_2/CH_2Cl_2) yielding 6.17 (390 mg, 92%). Mp 62.5-64.5 °C. Anal. Calcd for $C_{25}H_{32}O_5S$: C, 67.54; H, 7.25; S, 7.21. Found: C, 67.26; H, 7.30; S, 7.08; HRMS calcd 444.197, found 444.196.

[3R-[3α(1R*,2S*,5R*),3aα,7aα]]-3a,4,7,7a-Tetrahydro-5,6-dimethyl-3-[[5-methyl-2-(1-methylethyl)cyclohexyl]oxy]-3a-(phenylsulfonyl)-1(3H)-isobenzofuranone (6.20)

A solution of compound 6.2 (335 mg, 0.89 mmol) and 2,3-dimethyl-1,3-butadiene (6.19) (364 mg, 4.4 mmol) in dry benzene (25 mL) was refluxed for 20 h. After evaporation of the solvent under reduced pressure the product was purified by flash column chromatography (SiO_2/CH_2Cl_2, Rf = 0.53) yielding pure 6.20 (287 mg, 70%) as a single isomer. Mp 148.5-150.0 °C. ^1H NMR ($CDCl_3$, 300 MHz): δ 0.54 (d, J = 7.0 Hz, 3H), 0.63 (d, J = 7.0 Hz, 3H), 0.85 (m, 2H), 0.90 (d, J = 6.2 Hz, 3H), 1.05 (m, 1H), 1.10 (m, 1H), 1.30 (m, 2H), 1.47 (s, 3H), 1.53 (s, 3H), 1.60 (m, 2H), 2.11 (m, 2H), 2.43 (br.s, 2H), 2.87 (br.d, J = 19.0 Hz, 1H), 3.22 (m, 1H), 3.44 (dt, J = 4.0, 10.6 Hz, 1H), 5.37 (s, 1H), 7.46 (m, 2H), 7.58 (m, 1H), 7.95 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 14.86 (q), 18.56 (q), 18.82 (q), 20.60 (q), 22.04 (q), 22.68 (t), 24.95 (d), 27.04 (t), 31.27 (d), 31.56 (t), 34.12 (t), 38.30 (d), 38.47 (t), 47.26 (d), 67.91 (s), 100.91 (d), 120.84 (s), 123.31 (s), 128.21 (d), 130.04 (d), 133.72 (d), 137.11 (s), 174.71 (s); Anal. Calcd for $C_{26}H_{36}O_5S$: C, 67.65; H, 7.83; S, 6.94. Found: C, 67.65; H, 7.88; S, 6.96; HRMS (M^+ - $C_6H_5SO_2H$) calcd 318.219, found 318.218. $[\alpha]^D_{20}$ +161.4° (c 1.00, CH_2Cl_2)

Benzyltrimethylammonium iodide (6.22)

This compound was synthesized according to the procedure of Brasen and Hauser.[16] A solution of N,N-dimethylbenzylamine (67.5 g, 0.5 mol) in absolute ethanol (100 mL) was placed in a three-necked flask equipped with a dropping funnel, a reflux condenser and a mechanical stirrer. The openings of the dropping funnel and the reflux condenser were sealed with drying tubes. While the solution was stirred rapidly methyl iodide (95.0 g, 0.67 mol) was added at such a rate as to cause gentle refluxing of the solution. After the addition was completed the solution was for an additional 30 min. After cooling to room temperature anhydrous ether (500 mL) was added with stirring. The solid product (136.1 g, 99%) was removed by suction filtration and used without further purification in the next reaction step.

(o-Methylbenzyl)dimethylamine (6.23)

This compound was synthesized according to the procedure of Brasen and Hauser.[16] To liquid ammonia (400 mL) contained in a 1 L three-necked flask fitted with a mechanical stirrer and an air-cooled reflux condenser was added granulated ferric nitrate (0.25 g) and then sodium (13.9 g, 0.6 mol) was added in small pieces. Stirring was continued until the blue color had disappeared and a gray suspension remained. Benzyltrimethylammonium iodide (136.1 g, 0.5 mol) was added over a period of 15 min., resulting in a greenish solution. Stirring was continued for 2 h. while more ammonia was added to maintain the original volume. The ammonium chloride (13.5 g, 0.25 mol) was added. Water (about 150 mL) was added, dropwise at first. After the mixture had reached room temperature the solution was extracted with ether (3 x 100 mL). The combined ether solutions were washed with brine and dried over anhydrous potassium carbonate. After filtration and removal of the solvent under reduced pressure product 6.23 (63.45 g, 85%) was obtained as an oil, which was pure according to the ^{1}H NMR spectrum. ^{1}H NMR ($CDCl_3$, 60 MHz): δ 2.25 (s, 6H), 2.43 (s, 3H), 3.36 (s, 2H), 7.12 (s, 4H).

[o-((Trimethylsilyl)methyl)benzyl]dimethylamine (6.24)

According to the procedure of Saegusa *et al.*[7] To a solution of 6.23 (8.1 g, 55.1 mmol) in anhydrous ether (150 mL) was added *n*-butyl lithium (68.1 mL, 1.6 M solution) at 0 °C over a period of 30 min. Stirring was continued at room temperature for 22 h. To the solution was added a mixture of trimethylchlorosilane (17.5 mL, 138 mmol) and triethylamine (2 mL) at 0 °C at once, and the solution was stirred at room temperature for 4 h. Aqueous $NaHCO_3$ was added and the solution was extracted with ether. The combined organic layers were washed with water and brine, dried over $MgSO_4$ and evaporated. The residue was distilled (bp 69-70 °C (0.1 mm Hg)) to give 6.24 (11.18 g, 92%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 60 MHz): δ 0.10 (s, 9H), 2.32 (s, 8H), 3.37 (2H), 7.09 (m, 4H).

[o-((Trimethylsilyl)methyl)benzyl]trimethylammonium iodide (6.25)

According to the procedure of Saegusa *et al.*[7] A solution of amine 6.24 (11.18 g, 50.6 mmol) and methyl iodide (19.6 g, 138 mmol) in acetonitrile (150 mL) was refluxed for 1 h. Most of the solvent was removed by evaporation under reduced pressure. After the addition of a large amount of ether the precipitate was removed by filtration yielding product 6.25 (18.4 g, 100%) as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.09 (s, 9H), 2.48 (s, 2H), 3.55 (br.s, 9H), 4.88 (s, 2H), 6.97-7.81 (m, 4H).

[3R-[3α(1R,2S*,5R*),3aα,7aα]]-3a,4,9,9a-Tetrahydro-3-[[5-methyl-2-(1-methylethyl)-cyclohexyl]oxy]-3a-(phenylsulfonyl)-1(3H)-isonaphtofuranone (6.27)*

a) According to the procedure of Saegusa[7] for the preparation of 6.26.

To a stirred solution of furanone 6.2 (756 mg, 2.0 mmol) and compound 6.25 (726 mg, 2.0 mmol) in acetonitrile (40 mL) was added very slowly at room temperature a solution of tetrabutylammonium fluoride (631 mg, 2.0 mmol) in acetonitrile (40 mL). After evaporation of the solvent, ether was added and the solution was filtered over a short pad of silica gel. The crude reaction product 6.27 was purified by flash chromatography (SiO_2/CH_2Cl_2) yielding, after evaporation of the solvent under reduced pressure, a white foam (520 mg, 43%) which could not be crystallized. Mp 90-95 °C.

Spectroscopic data were in complete agreement with those reported in the following experiment (*vide infra*).

b) According to the procedure of Boudjouk and Han[8] for the preparation of 6.26.

A mixture of 6.2 (378 mg, 1.00 mmol), α,α'-dibromo-*o*-xylene (6.28) (260 mg, 0.98 mmol) and activated zinc (150 mg, 2.29 mmol) were dissolved in dry dioxane (1 mL) under an inert atmosphere of nitrogen. After reaction for 4 h at room temperature in an ultrasound cleaning bath water was added and the resulting mixture was extracted with ether. The combined organic layers were dried over $MgSO_4$, filtered and the solvent evaporated under reduced pressure. The crude product 6.27 (single isomer by ^1H NMR) was purified by flash column chromatography (CH_2Cl_2/SiO_2, Rf = 0.56). After evaporation of the solvent analytically pure product was obtained as a white foam. Yield 50%. The product could not be recrystallized from solvents like *n*-hexane or petroleum-ether 40-60. $[\alpha]^{20}_D$ +153.8° (c 1.00, CH_2Cl_2); ^1H NMR ($CDCl_3$, 300 MHz): δ 0.59 (d, J = 6.6 Hz, 3H), 0.66-0.98 (m, 3H), 0.76 (d, J = 7.3 Hz, 3H), 0.89 (d, J = 6.2 Hz, 3H), 1.20 (m, 2H), 1.61 (m, 2H), 1.72 (m, 1H), 1.86 (br.d, 1H), 3.02 (d, J = 15.7 Hz, 1H), 3.11 (dd, J = 6.6, 15.4 Hz, 1H), 3.28 (dd, J = 1.8, 15.7 Hz, 1H), 3.32 (dt, J = 4.4, 10.8 Hz, 1H), 3.71 (d, J = 15.7 Hz, 1H), 3.84 (dd, J = 1.8, 6.6 Hz, 1H), 5.17 (s, 1H), 7.17 (m, 4H), 7.54 (m, 2H), 7.65 (m, 1H), 7.98 (d, J = 7.3 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 14.94 (q), 20.82 (q), 22.04 (q), 22.62 (t), 24.74 (d), 28.37 (t), 31.18 (d), 31.94 (t), 34.03 (t), 39.10 (t), 42.09 (d), 47.26 (d), 70.88 (s), 79.03 (d), 102.39 (d), 127.34 (d), 127.42 (d), 128.05 (d), 128.34 (d), 128.41 (d), 130.88 (d), 131.48 (s), 133.75 (s), 133.84 (d), 137.43 (s), 173.60 (s); Anal. Calcd for $C_{28}H_{34}O_5S$: C, 69.68; H, 7.10; S, 6.64. Found: C, 69.48; H, 7.21; S, 6.26.

General experiment for gel formation

A weighted amount of compound 6.27 in an organic solvent was heated in a thick-wall test tube with an internal diameter of 1.5 cm (for a volume less than 10 mL) or 2.5 cm (for volumes more than 10 mL) until all the solid dissolved. The solution was then left to cool to ambient temperature or in an ice bath to 0 °C. Gel formation was observed while cooling or immediately after the cooling process. Gelation was considered successful when inverted, the sample did not flow perceptibly. Dilution of the solution followed by heating was repeated until no longer gel formation was observed or a two layer system of gel and solvent was formed. When the solution of 6.27 is cooled slowly an almost complete transparent gel is obtained.

[3R-[3α(1R*,2S*,5R*),3aα,8aα]]-3a,4,8,8a-Tetrahydro-3-[[5-methyl-2-(1-methylethyl)-cyclohexyl]oxy]-3a-(phenylsulfonyl)-1(3H)-thieno[2,3-f]isobenzofuranone (6.31a) and [3R-[3α(1R*,2S*,5R*),3aα,8aα]]-3a,4,8,8a-tetrahydro-3-[[5-methyl-2-(1-methylethyl)cyclohexyl]oxy]-3a-(phenylsulfonyl)-1(3H)-thieno[3,2-f]isobenzofuranone (6.31b)

To a stirred solution of 6.29 (350 mg, 0.95 mmol) and dienophile 6.2 (360 mg, 0.95 mmol) in acetonitrile (40 mL) was added, at room temperature, a solution of tetrabutylammonium fluoride·$3H_2O$ (360 mg, 1.14 mmol) in acetonitrile (40 mL) in the course of 2 h. Workup by concentrating the solution by distillation, addition of Et_2O, filtration and removal of the solvent gave a dark colored oil. Purification by filtration over silica gel (Et_2O) gave a 1:1 mixture of 6.31a and 6.31b (409 mg, 88%) as a slightly yellow solid, which was pure according to ^{13}C NMR spectroscopy. Attempts to separate the isomeric mixture by flash chromatography or by crystallization were not

successful. Analytically pure material (still as a mixture of isomers) was obtained by crystallization from hexane. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.60 (d, J = 7.0 Hz, 3H), 0.70 (d, J = 7.0 Hz, 3H), 0.98 (d, J = 7.0 Hz), 0.75-1.02 (m, together with doublet 5H), 1.03-1.55 (m, 4H), 1.58-1.71 (m, 2H), 2.10 (m, 1H), 2.79 (d, J = 17.6 Hz, 0.5H), 2.98 (d, J = 19.1 Hz, 0.5H), 3.06 (dd, J = 7.7, 17.5 Hz, 0.5H), 3.23 (dd, J = 8.0, 18.2 Hz, 0.5H), 3.33 (d, J = 18.2 Hz, 0.5H), 3.48 (d, J = 17.5 Hz, 0.5H), 3.48-3.58 (m, 1.5H), 3.61 (d, J = 7.7 Hz, 0.5H), 3.75 (d, J = 19.1 Hz, 0.5H), 3.89 (d, J = 17.6 Hz, 0.5H), 5.49 (s, 0.5H), 5.51 (s, 0.5H), 6.59 (d, J = 4.3 Hz, 0.5H), 6.72 (d, J = 4.4 Hz, 0.5H), 7.04 (m, 1H), 7.42-7.52 (m, 2H), 7.56-7.64 (m, 1H), 7.86-7.94 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 14.91 (q), 20.70 (q), 21.17 (t), 21.78 (t), 22.10 (q), 22.73 (t), 25.09 (d), 26.22 (t), 26.94 (t), 31.35 (d), 34.17 (t), 38.57 (t), 39.24 (d), 39.80 (d), 47.37 (d), 68.38 (s), 68.90 (s), 77.47 (d), 77.51 (d), 100.84 (d), 101.05 (d), 123.30 (d), 123.56 (d), 126.03 (d), 126.64 (d), 128.41 (d), 129.28 (s), 129.35 (s), 130.20 (d), 130.26 (d), 130.75 (s), 130.87 (s), 134.02 (d), 134.06 (d), 136.65 (s), 136.70 (s), 173.60 (s), 173.89 (s); HRMS calcd 488.169, found 488.170; Anal. Calcd for $C_{26}H_{32}O_5S_2$: C, 63.91; H, 6.60; S, 13.12. Found: C, 64.07; H, 6.76; S, 12.85.

[1R-[1α(3S*,5R*),2B,5α]]-Dihydro-5-[[5-methyl-2-(1-methylethyl)cyclohexyl]oxy]-3-(4-methyl-phenylthio)-2(3H)-furanone (6.34)

To a stirred solution of diisopropylamine (0.32 mL, 2.28 mmol) in dry THF (10 mL) at -40 °C, under an inert atmosphere of nitrogen, was added a butyllithium solution (1.40 mL, 1.6 M in *n*-hexane, 2.24 mmol). After stirring for 10 minutes the solution was cooled to -80 °C and dihydro-2(3H)-furanone 6.32 (480 mg, 2.00 mmol) was added. After stirring the solution for 0.5 h at this temperature, thiosulfonic S-ester 6.33 (612 mg, 2.20 mmol), dissolved in dry THF (5 mL) was added. Stirring was continued for 0.5 h, water was added and the resulting mixture was extracted with ether (3 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and the solvent evaporated under reduced pressure. The residue was distilled (250 °C, 0.001 mm Hg) yielding product 6.34 (420 mg, 58%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.72-1.05 (m, 12H), 1.17 (m, 1H), 1.32 (m, 1H), 1.61 (m, 2H), 1.98 (m, 2H), 2.28 (m, 1H), 2.34 (s, 3H), 2.44 (ddd, J = 1.9, 8.4, 13.6 Hz, 1H), 3.46 (dt, J = 4.1, 10.6 Hz, 1H), 3.97 (t, J = 8.7 Hz, 1H), 5.48 (dd, J = 1.9, 5.4 Hz, 1H), 7.13 (d, J = 8.4 Hz, 2H), 7.42 (d, J = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 15.21 (q), 20.58 (q), 20.83 (q), 21.89 (q), 22.66 (t), 25.07 (d), 30.93 (d), 33.89 (t), 36.27 (t), 39.38 (t), 44.21 (d), 47.29 (d), 76.56 (d), 98.04 (d), 127.41 (s), 129.63 (d), 134.00 (d), 138.64 (s), 173.89 (s).

Attempted chlorination of 6.34

To a solution of compound 6.34 (420 mg, 1.16 mmol) in carbon tetrachloride (25 mL) was added N-chlorosuccinimide (170 mg, 1.28 mmol) and the resulting mixture was refluxed for 20 h. According to the ^{1}H NMR of the crude reaction mixture no reaction had occurred.

[1R-[1α(3S*,5R*),2B,5α]]-Dihydro-5-[[5-methyl-2-(1-methylethyl)cyclohexyl]oxy]-3-iodo-2(3H)-furanone (6.36)

To a stirred solution of diisopropylamine (0.42 mL, 3.0 mmol) in dry THF (10 mL) at -40 °C, under an inert atmosphere of nitrogen, was added a *n*-butyllithium solution (1.88 mL 1.6 M in *n*-hexane, 3.0 mmol). After stirring for 15 minutes at -40 °C the

solution was cooled to -78 °C and compound 6.32 (480 mg, 2.0 mmol) was added. Stirring was continued for 0.5 h. The reaction mixture was added through a septum to a solution of iodide (762 mg, 3.0 mmol) in dry THF (25 mL), which had been cooled to -78 °C. Stirring was continued for 15 minutes at this temperature. Ether was subsequently added to the reaction mixture. The solvent was extracted with water containing sodium thiosulfate, dried over $MgSO_4$ and evaporated under reduced pressure. Product 6.36 (615 mg, 84%) was obtained as a yellow solid which turned dark upon standing in the air. Analytically pure 6.36 was obtained by crystallization from *n*-hexane. Mp 84.0-85.2 °C (dec.); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.72-1.04 (m, 12H), 1.18 (m, 1H), 1.35 (m, 1H), 1.63 (m, 2H), 2.04 (m, 2H), 2.62 (m, 2H), 3.53 (dt, J = 4.4, 10.6 Hz, 1H), 4.71 (t, J = 4.71 Hz, 1H), 5.76 (t, J = 4.4 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 8.56 (d), 15.55 (q), 20.78 (q), 22.09 (q), 22.93 (t), 25.33 (d), 31.22 (d), 34.09 (t), 39.69 (t), 42.13 (t), 47.55 (d), 77.84 (d), 100.56 (d), 173.23 (s); Anal. Calcd for $C_{14}H_{23}IO_3$: C, 45.91; H, 6.33; I, 34.65. Found: C, 45.58 ; H, 6.38; I, 34.21.

[1R[1α(4R*,5R*),2B,5α]]-4-Chloro-dihydro-3-methyl-5-[[5-methyl-2-(1-methylethyl)cyclohexyl]-oxy]-4-(phenylthio)-2(3H)-furanone (6.39)

A mixture of (5R)-5-(*l*-menthyloxy)-3-methyl-2(5H)-furanone (6.37) (252 mg, 1.00 mmol), thiophenol (121 mg, 1.10 mmol) and 3 drops of triethylamine was heated until a homogeneous mixture was obtained. Heating was repeated when solid material appeared again. After 1 h a complete conversion had occurred as was deduced from the ^{1}H NMR spectrum of the reaction mixture. The excess thiophenol and triethylamine were removed under high vacuum (0.05 mm Hg) yielding a white solid material. The crude reaction product was dissolved in carbon tetrachloride (25 mL) and after the addition of N-chlorosuccinimide (147 mg, 1.10 mmol) the solution was refluxed for 1.5 h. The solvent was removed under reduced pressure and *n*-hexane was added. The mixture was refluxed for a short time and the solid material was removed by filtration. The *n*-hexane was removed by evaporation under reduced pressure and the resulting solid material was crystallized from *n*-hexane yielding product 6.39 (190 mg, 50% overall) as a white crystalline compound. Mp 118.1-122.1 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.72 (d, J = 7.0 Hz, 3H), 0.87 (d, J = 7.7 Hz, 3H), 0.91 (d, J = 6.6 Hz, 3H), 0.80-1.06 (m, 3H), 1.31 (m, 2H), 1.34 (d, J = 7.0 Hz, 3H), 1.66 (m, 2H), 1.94 (m, 2H), 3.16 (q, J = 7.0 Hz, 1H), 3.58 (dt, J = 4.0 Hz, 10.6 Hz, 1H), 5.48 (s, 1H), 7.38 (m, 3H), 7.68 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 9.64 (q), 15.38 (q), 20.74 (q), 22.04 (q), 22.96 (t), 25.51 (d), 31.18 (d), 34.08 (t), 38.90 (t), 45.33 (d), 47.57 (d), 77.19 (d), 84.53 (s), 102.84 (d), 128.34 (s), 128.65 (d), 129.96 (d), 136.55 (d), 174.10 (s).

[1S[1α(S*),2B,5α]]-3-Methyl-5-[[5-methyl-2-(1-methylethyl)cyclohexyl]oxy]-4-(phenylthio)-2(5H)-furanone (6.40)

Compound 6.39 (160 mg, 0.42 mmol) was dissolved in triethylamine (10 mL) and heated for 15 min under reflux. The solvent was evaporated under reduced pressure, and water (25 mL) and CH_2Cl_2 (15 mL) were added. The water layer was extracted with CH_2Cl_2 (3 x 15 mL). The combined organic layers were dried over $MgSO_4$, filtered and the solvent evaporated under reduced pressure yielding product 6.40 as a colorless oil (single isomer by ^{1}H NMR). The product was crystallized from *n*-hexane at -25 °C yielding 6.40 (124 mg, 85%) as fine white needles. Mp 83.7-84.5 °C. ^{1}H

NMR ($CDCl_3$, 300 MHz): δ 0.55-0.89 (m, 2H), 0.68 (d, J = 6.6 Hz, 6H), 0.76 (d, J = 7.0 Hz, 3H), 0.97-1.18 (m, 4H), 1.50 (m, 2H), 1.74 (d, J = 1.1 Hz, 3H), 2.01 (m, 1H), 3.34 (dt, J = 4.0, 10.6 Hz, 1H), 5.62 (q, J = 1.1 Hz, 1H), 7.32 (m, 3H), 7.45 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 9.28 (q), 15.46 (q), 20.74 (q), 21.93 (q), 22.75 (t), 24.87 (d), 30.99 (d), 33.91 (t), 38.79 (t), 47.35 (d), 78.57 (d), 98.03 (d), 125.13 (s), 128.11 (s), 129.20 (d), 129.24 (d), 134.19 (d), 154.17 (s), 170.47 (s); HRMS calcd 360.176, found 360.176.

[1S[1α(S*),2β,5α]]-3-Methyl-5-[[5-methyl-2-(1-methylethyl)cyclohexyl]oxy]-4-(phenylsulfonyl)-2(5H)-furanone (6.41)

Compound 6.40 (120 mg, 0.33 mmol) was dissolved in CCl_4 (5 mL) and *m*-CPBA (144 mg, 0.86 mmol) was added. After stirring for 15 minutes at room temperature a complete conversion to compound 6.41 had occurred (based on ^1H NMR). The solution was filtered, the organic phase was evaporated under reduced pressure and *n*-hexane was added. After brief heating of the solution the remaining solid was removed by filtration, and the solvent was removed by evaporation under reduced pressure. Crude 6.41 was purified by flash column chromatography (SiO_2/CH_2Cl_2, Rf = 0.39) yielding pure 6.41 (76 mg, 58%) as a white crystalline compound. $[\alpha]^{20}_D$ -169.7° (c 1.53, CH_2Cl_2); ^1H NMR ($CDCl_3$, 300 MHz): δ 0.62 (d, J = 7.0 Hz, 3H), 0.72 (d, J = 7.0 Hz, 3H), 0.80-1.06 (m, 4H), 0.97 (d, J = 6.2 Hz, 3H), 1.58 (m, 1H), 1.65 (m, 3H), 2.25 (m, 1H), 2.28 (d, J = 1.5 Hz, 3H), 3.59 (dt, J = 4.4, 10.6 Hz, 1H), 6.24 (d, J = 1.5 Hz, 1H), 7.59 (m, 2H), 7.68 (m, 1H), 7.94 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 10.07 (q), 15.52 (q), 20.55 (q), 22.11 (q), 23.00 (t), 24.95 (d), 31.27 (d), 34.06 (t), 38.94 (t), 47.75 (d), 79.03 (d), 97.40 (d), 128.39 (d), 128.91 (d), 134.32 (d), 134.32 (s), 139.34 (s), 139.82 (s), 151.51 (s), 168.80 (s); HRMS could not be determined as M^+ was not observed.

Attempted Diels-Alder reaction between dienamine 6.43 and furanone 6.2

A solution of diene 6.43 (219 mg, 1.00 mmol) and furanone 6.2 (378 mg, 1.00 mmol), dissolved in dry toluene (10 mL), was refluxed for 20 h. As the heating was started the solution turned brown. After evaporation of the solvent under reduced pressure no product could be isolated.

Attempted Diels-Alder reaction between dienolether 6.44 and furanone 6.2

A solution of compound 6.44 (360 mg, 2.0 mmol) and furanone 6.2 (378 mg, 1.0 mmol), dissolved in dry toluene (5 mL), was refluxed for 20 h. After evaporation of the solvent under reduced pressure a mixture of both starting compounds were recovered unchanged.

Attempted Diels-Alder reaction between trimethylsilyldienolether 6.45 and furanone 6.2

A solution of furanone 6.2 (246 mg, 0.65 mmol) and diene 6.45 (238 mg, 1.00 mmol) in dry benzene (5 mL) were heated for 3 days at 80 °C. After evaporation of the solvent the furanone 6.2 was recovered. The reaction was repeated in refluxing xylene (140 °C), but also under these reaction conditions no cyclization product was obtained.

6.13 *References*

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